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ANTIGEN-SPECIFIC ANTIBODIES APPLICATION ON TUBERCULOSIS

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Abstract
Tuberculosis (TB) is caused by Mycobacterium tuberculosis (Mtb). Mtb is an airborne transmitted pathogen, and the immune responses, especially the mucosal immune response, play fundamental roles for the host to defend the primary and the containment of Mtb infection. It remains a significant health threat to mankind and is undoubtedly the most successful disease caused by a single infectious agent ever. TB killed ~1.5 million individuals in 2018 alone, and a total of around 1,000,000,000 people over the last 200 years. The Bacillus Calmette-Guerin immunization is the as it was authorized immunization against TB, but its protective impact does not amplify to controlling the improvement of irresistible pulmonary disease in grown-ups. To develop improved vaccines and a new method for controlling TB, an important element is the discovery of markers to measure the effectors' mechanisms of the protective immune response against M. tuberculosis. Humoral responses are conspicuous during active TB illness and have indeed been hypothesized to contribute to immunopathology. In any case, there's proof to recommend that particular antibodies may restrain the dispersal of MTB, and possibly play a part in the avoidance of disease through mucosal resistance. Further, antibodies are now understood to confer protection against a run of intracellular pathogens by modulating immunity via means of Fc-receptor mediated phagocytosis. The objective of the present study will be to review antigen-specific antibodies application in Tuberculosis and their potential utility as biomarkers and their functional contribution to Mtb control.

Keywords: antibodies, humoral immunity, tuberculosis

Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), remains a significant health threat to mankind and is undoubtedly the most successful disease caused by a single infectious agent ever (Cardona, 2016). TB killed ~1.5 million individuals in 2018 alone, and a total of around 1,000,000,000 people over the last 200 years (WHO, 2019; Paulson, 2013).

Approximately one-fourth to one-third of the world's population is infected with Mtb, giving rise to an estimated 10 million new cases annually (WHO, 2019). Mtb infection

leads to a spectrum of infectious states ranging from various levels of asymptomatic states, collectively referred to as latent tuberculosis infection (LTBI) and a spectrum of active tuberculosis diseases (ATB), ranging from local to pulmonary to disseminating ATB (Kawahara et al., 2019; Demartino, 2019). About 5 10% of individuals with LTBI will progress to ATB during their lifetime; the remainder can contain the infection lifelong unless immunosuppressed, such as by co-infecting viruses [e.g., human immunodeficiency virus (HIV)] or iatrogenically (Cardona, 2016; Joosten et al., 2013).

It is assist evaluated that 2 billion individuals right now keep up an inactive infection with Mycobacterium tuberculosis the causative agent of TB, and are subsequently at the chance of creating active disease at a few points during their lives (Clemens Hermann and Carolyn G. King, 2021). Thus, the development of rapid and accurate new diagnostic methods is vital for the global control of TB. However, the diagnostic accuracy of existing tests is inadequate (Wallis et al., 2013).

The Bacillus Calmette Guerin (BCG) antibody was presented to avoid disease during the mid-20th century but, despite far-reaching scope, has fizzled (Ashley et al., 2016). This arm of the resistant framework has been explored

during normal infection with Mycobacterium tuberculosis in detail (Flynn, 2001; Nunes-Alves et al., 2014); and even though imperative, isn't fundamentally adequate to avoid the microbes.

As a facultative intracellular bacterium that resides primarily in lung alveolar macrophages, the vast majority of TB research efforts have traditionally focused on understanding cell-mediated immunity (CMI)(Cooper, 2009; Ottenhoff, 2012), By contrast, the role of B-cell and antibody-mediated immunity (AMI) in TB has remained understudied for decades. This was due to the historical dogma, established in the early twentieth century, that postulated that host defense against intracellular pathogens is mediated by CMI, whereas the response to extracellular pathogens is mediated by Abs produced from B-cells (Kawahara et al., 2019; Csadevall, 2018). The MVA85A is one such vaccine and was as of late tried in two points of interest adequacy trials (Tameris et al., 2013; Ndiaye et al., 2015).

As Mycobacterium tuberculosis may be a facultative intracellular pathogen, it has been hypothesized that antibodies either have no protective advantage or may indeed contribute to immunopathology inactive infection (Orme, 2014). Surmounting this presumed lack of functional antibodies in TB presents a significant challenge for the next generation of immunizations against TB, as antibody titer and specificity remain the overwhelming connections of vaccine-mediated immunity for numerous other illnesses (Plotkin, 2008). In this manner, the objective of this paper is to review antigen-specific antibodies application in Tuberculosis and their potential utility as biomarkers, and their functional contribution to Mtb control.

2. Tuberculosis

Mycobacterium tuberculosis infection in people produces a range of clinical and subclinical infections (Milla *et al*., 2019). This continuum can be freely gathered into active TB, subclinical TB, latent TB, inactive TB, and "Resisters." People with active TB have distinguishable bacillary burden by culture or PCR and commonly have a positive interferon-γ (IFN-γ) releasing assay (IGRA) or tuberculin skin test (TST) with cough, weight loss, and fever (Milla *et al*., 2019).

Subclinical TB is characterized as an asymptomatic illness but with a misfortune of bacterial control which can be watched with aggravation as identified radiographically by positron emission tomography (PET) (Milla *et al*., 2019). At the other conclusion of the range, inactive TB is distinguished as tireless asymptomatic contamination, TST or IGRA positive with no transmission capacity (Achkar and Jenny-Avital, 2011).

Not at all like subclinical TB, do people with inactive disease not illustrate zones of PET eagerness reliable with active illness (Milla *et al*., 2019). At last, a subset of TST and IGRA negative people have been recognized called "Resisters" who show up to have non-canonical safe reactions to mycobacterium tuberculosis antigens within the setting of high levels of introduction (Simmons *et al*., 2018).

2.1. Life Cycle of Mycobacterium Tuberculosis.

Person-to-person transmission occurs by inhalation of aerosolized droplets generated by a person with active disease. Bacteria travel to the lungs, where they are taken up by alveolar macrophages. Inside the alveolar macrophages, bacteria are exposed to reactive oxygen (ROS) and nitrogen species generated by macrophages. M. tuberculosis can evade macrophage killing by inhibiting phagosome-lysosome fusion. This leads to the recruitment of immune cells, which contributes to the formation of granulomas that can contain M. tuberculosis. In 90% of the cases, infected individuals contain the infection within the granuloma, where the bacteria can survive in a nonreplicating state, probably triggered by hypoxic and nutrient-starved conditions. In around 10% of cases, the disease will progress and develop into active disease, which can lead to the release of M. tuberculosis from the granulomas. In a small percentage of latently infected individuals, the disease can reactivate later in life leading to the development of active disease.

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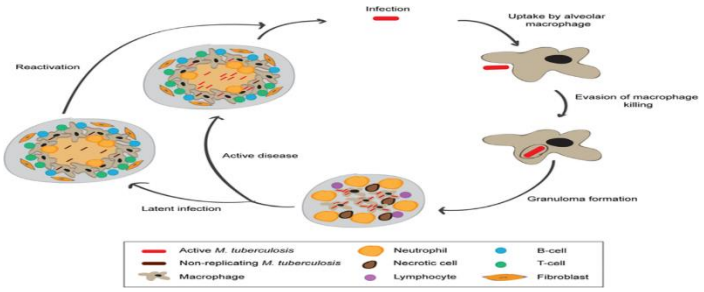

Figure 1: Schematic representation of the life cycle of M. tuberculosis

Person-to-person transmission occurs by inhalation of aerosolized droplets generated by a person with active disease. Bacteria travel to the lungs, where they are taken up by alveolar macrophages. Inside the alveolar macrophages, bacteria are exposed to reactive oxygen (ROS) and nitrogen (NOS) species generated by macrophages. M. tuberculosis can evade macrophage killing by inhibiting phagosome-lysosome fusion. This leads to the recruitment of immune cells, which contributes to the formation of granulomas that can contain M. tuberculosis. In 90% of the cases, infected individuals contain the infection within the granuloma, where the bacteria can survive in a non-replicating state, probably triggered by hypoxic and nutrient-starved conditions. In around 10% of cases, the disease will progress and develop

into an active disease, which can lead to the release of M. tuberculosis from the granulomas. In a small percentage of latently infected individuals, the disease can reactivate later in life leading to the development of active disease. (<a href="https://www.researchgate.net/figure/).

2.2. Pathogenesis of Mycobacterium Tuberculosis

Mycobacterium tuberculosis is an airborne pathogen. Once inhaled, droplets bearing the mycobacteria settle throughout the airways. Most of the bacilli are trapped in the upper parts of the airways where the mucus-secreting goblet cells are located.

The mucus catches the invading bacilli, and the cilia on the surface of the cells constantly undulate to move the mucus and trap foreign particles upward for removal (Frieden *et al*., 2003).

The bacteria that can pass the mucociliary system and reach the alveoli are quickly engulfed by alveolar macrophages. This next line of defense is the innate immune system, and it provides an opportunity for the body to destroy the invading mycobacteria and prevent the infection. The complement system plays a key role in the phagocytosis of the bacteria. The complement protein C3 binds to the cell wall and enhances recognition of the mycobacteria by macrophages**.** Opsonization by C3 is fast, even in the airspaces of a host with no previous exposure to M. tuberculosis (Vancrevel *et al*., 2002). The phagocytosis by macrophages initiates a cascade of events that results in either effective control of the infection (which may be followed by latent tuberculosis) or progression to active disease, called primary progressive tuberculosis.

After being swallowed by macrophages, the mycobacteria continue to multiply slowly, with bacterial cell division occurring every 25 to 32 hours. The initial development involves the production of proteolytic enzymes and cytokines by macrophages to try to degrade the bacteria. The cytokines that are released attract T lymphocytes to the site; T cells now lead the cell-mediated immunity. Macrophages present mycobacterial antigens on their surface to the T cells (Dhedak *et al*., 2005)**.**

For those individuals with intact cell-mediated immunity, the next defensive step is the formation of granulomas around the M. tuberculosis organisms. These nodular-type lesions, called Ghon complexes, form from an accumulation of activated T cells and macrophages that limit replication and the mycobacteria's spread. This destroys the macrophages and produces necrosis at the center of the lesion, yet the bacteria can survive since M. tuberculosis can change their phenotypic expression to enhance survival.

By 2 to 3 weeks, the necrotic environment resembles soft cheese, often referred to as caseous necrosis (Du Toit *et al*., 2006). The conditions for this necrosis include low pH and limited nutrients. These conditions restrict further growth and the lesions undergo fibrosis and calcification, successfully controlling the infection and causing the bacteria to enter a dormant form**.**

For immune-compromised individuals, granuloma formation is initiated but ultimately is unsuccessful in containing the bacteria. The necrotic tissue undergoes liquefaction and the fibrous wall of the granuloma loses structure. The liquefied necrotic material may then move into a bronchus or nearby blood vessel. If M. tuberculosis discharges into a vessel, extra-pulmonary tuberculosis is most likely to occur. Bacilli can also drain into the lymphatic system and collect in the trachea-bronchial lymph nodes of the affected lung, where the organism can form new caseous granulomas (Knecha *et al*., 2009).

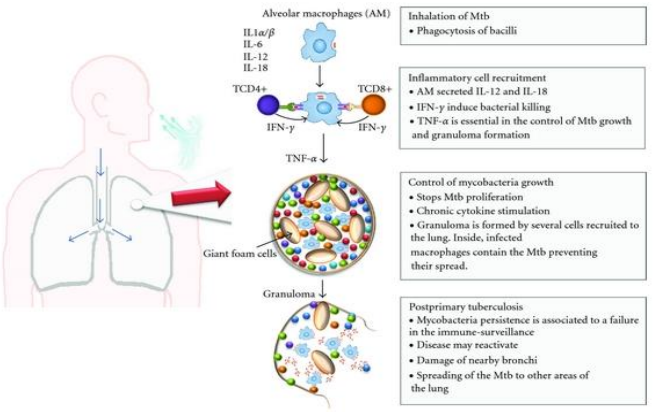

Figure 2: Pathogenesis of tuberculosis

TB pathogenesis can be divided into four well-defined events. Inhalation of the mycobacteria is followed by its interaction with resident macrophages through cellular r eceptors and its internalization. Macrophage bactericidal m echanisms are then activated, including RNI and ROI gene ration. The efficient killing of mycobacteria depends on pa thogen and host factors. Inflammatory cell recruitment: sur vived mycobacteria proliferate within macrophages inducing the production of proinflammatory cytokines. The local inflammatory environment induces the recruitment of several cell types including monocytes, neutrophils, and dendritic cells to the site of infection. High levels of TNF-α contribute to controlling Mtb growth and granuloma formation. Control of mycobacteria proliferation: the arrival of immune cells to the site of infection including T cells, which become organized in characteristic structures called granulomas efficiently stop mycobacteria proliferation and contain the mycobacteria within the granuloma walls preventing its spread. Characteristic of this structure is the presence of foam cells resulting from the differentiation of chronically activated macrophages. Mycobacteria containment eventually becomes a stable (latent) infection. Post-primary TB: mycobacteria persistence associated with a failure in the immunosurveillance system increases the risk that latent disease becomes reactivated, inducing the damage of nearby bronchi and conditioning the spreading

of the Mtb to other areas of the lung and the transmission of the disease (Joaquin *et al*., 2012).

2.3. Cell-Mediated Immune Responses in Tuberculosis

2.3.1. Initiation of the T cell Response

The effector function of antigen-specific cells is an indicator of the initiation of the cellular response and dissemination of bacteria to the draining lymph node that occurred following aerosol infection (Chackeran *et al*., 2002). The draining lymph node was the first site of expression of effector function followed by the spleen and the lung. The temporal correlation between lymphocyte activation and bacterial arrival in the lymph node was taken to mean that acquired cellular immunity was initiated in the draining lymph node by bacteria disseminating from the lungs via the lymphatic drainage and that further dissemination occurred systemically thereafter (Chackeran *et al*., 2002).

The involvement of the dendritic cell in the migration of bacteria to the lymph node is assumed to be an essential element of the initiation of the response. MTB infected dendritic cells delivered to the lung via the intratracheal route are capable of migrating to the draining lymph node and initiating cellular responses (Khader *et al*., 2006). It is however unlikely that these cells are deposited in the alveolar space and indeed it is not known if they represent the functional aspects of the dendritic cells that occupy this unique environment. It is thought that conducting airway dendritic cells are active samplers of the mucosal environment and migrate readily to the draining node (Xia *et al*., 1995; Holt *et al*., 1994). In contrast, a dendritic cell within the alveolar tissue is in a regulated environment with surfactant protein and alveolar macrophages that may limit their ability to respond to infection and migrate to the lymph node as rapidly as would dendritic cell in the airway tissue (Demangel *et al*., 2002)

2.3.2. Development of Cellular Responses

Dendritic cells are currently considered to be the most efficient inducers of activation in naive T cells and to do this they provide not only the antigen-specific stimulus but also secondary and tertiary signals that promote efficient development of effector T cells. The impact of mycobacterial infection on dendritic cell function has been studied extensively. Indeed, the classic demonstration that immature dendritic cells can phagocytose particles and become efficient antigen-presenting cells used BCG as the maturation agent (Inaba *et al*., 1993). More recently however the ability of MTB to interfere with T cell stimulation has been suggested by the fact that dendritic cells infected *in vivo* are less efficient at stimulating antigen-specific T cells than are equivalent uninfected dendritic cells (Wolf *et al*., 2007). Both the innate and acquired response to MTB infection depends to a large degree on the recognition of MTB as a pathogen by the pattern recognition receptors.

2.3.3. Memory T cell Responses

The best way to accelerate the kinetics of acquired cellular responses is to expose the adaptive cells to specific antigens of the pathogen in an environment that will generate long-lived antigen-specific cells capable of 'remembering' the pathogens upon subsequent challenge; this is of course the basis of vaccination (Andrea, M. C, 2009). While we know that vaccination is an excellent way to protect against some diseases (primarily those controlled by antibodies) vaccination against tuberculosis is not generally protective against pulmonary disease in adults (Colditz *et al*., 1994). In contrast, vaccination can significantly limit the dissemination of disease to other organs and does protect children from disease sequellae such as tuberculous meningitis (Trunz *et al*., 2006).

2.4. Mechanisms of T cell Evasion in Tuberculosis

M. tuberculosis possesses multiple mechanisms to perturb innate immunity (Cambier *et al*., 2014). By disrupting innate responses, such as phagosome maturation (Mehra *et al*., 2013), apoptosis (Velmurugan *et al*., 2007), and autophagy (Ouimet *et al*., 2016), or by inducing detrimental type I interferon secretion (Mayer-Barber *et al*., 2011) or excessive TNF (Roca and Ramakrishnan, 2013). M. tuberculosis optimizes its early survival and modulates adaptive immunity to its advantage. Underlying the prolonged MTB latency in the host is not only the inhibition of macrophage phagocytosis, lysosome maturation, and acidification but also the inhibition of oxidative stress and the Function of Reactive Oxygen and Reactive Nitrogen Intermediates (Weijie, Z *et al*., 2019).

Since M. tuberculosis infects professional antigen-presenting cells, the bacteria are ideally located to perturb the functions of these cells. One target is the MHC class II antigen presentation pathway (hereafter termed the MHC II pathway), which is essential for antigen activation of CD4 T cells.

Initially described as sequestration of antigens produced b y intramacrophage mycobacteria from human CD4 T cells (Pancholi *et al*., 1993), multiple mechanisms contribute to a reduced recognition of M. tuberculosis-infected cells by antigen-specific CD4 T cells.

The formation of granulomas is a primary host defense mechanism for containing bacteria (Silva, M *et al*., 2012). The components of granulomas are compact, comprising aggregates of immune cells, including lymphocytes on the outside surrounding blood-derived infected and uninfected macrophages, foamy macrophages, epithelioid cells, and Langerhans cells (Guirado, E and Schlesinger, L.S, 2013). When they play a role as a primary host-defense mechanism for containing bacteria, they also provide a shelter for MTB, some of which can live dormant in these structures for a long time until an opportunity arises for re-activation and spread (Weijie Zhai *et al*., 2019).

2.5. Glycosylation Patterns in Mycobacterium Tuberculosis

Post-translational alterations of antibodies such as glycosyl ation are connected to inflammation. Antibody glycosylati on designs can be connected to TB in arrange to recognize inactive from dynamic TB (Milla *et al*., 2019). In the zone of autoimmunity, glycosylation of IgG has been broadly examined as a biomarker of disease severity. There is a higher binding of polyclonal IgG to FcγRIIIa on NK cells along with enhanced TB-specific ADCC in latent compared to active TB (Lu *et al*., 2016). In differentiating to IgG, the glycosylation of pentameric IgM is far more complex (Moh *et al*., 2016) and so less well-characterized and caught on (Milla *et al*., 2019).

3. Humoral immunity during tuberculosis infection

3.1. B cells and Tuberculosis Antibody Responses Based on the concept of division of labor by the cell-mediated and the humoral arm of the immune response in controlling pathogens, protection against intracellular microbes is generally thought to be mediated exclusively by cell-mediated immunity (Casadevall, 2003). This has led to the use of highly T cell-centric strategies for the development of vaccines against intracellular pathogens including M. tuberculosis (Sender and Hill, 2000).Although antibodies are induced against a broad range of protein and non-protein antigens in active TB disease, they are not useful for diagnosis due to a lack of sensitivity and specificity. There is evidence for reduced antibody avidity in active TB disease and perturbation in Fc receptor expression, suggesting that phagocytosis and antibody-mediated cellular cytotoxicity could be dysregulated. Transcriptomic signatures for B cells are also depressed in TB, suggesting down-regulation or exhaustion of the B cell response (Scriba *et al*., 2017).

B cells and antibodies are involved in the immune response to TB, and the interaction of antibodies with phagocytic cells through Fc receptor engagement is emerging as a key area for research. The quantity of antibodies produced during M. tuberculosis infection is related to bacterial load, and higher antibody responses are observed in those at risk of disease and are correlated with the mycobacterial load during disease (Kunnath *et al*., 2012). This suggests that antibodies are important in the control of active TB disease and has also led to the development of antibody-based assays for TB diagnosis (Scriba *et al*., 2017).

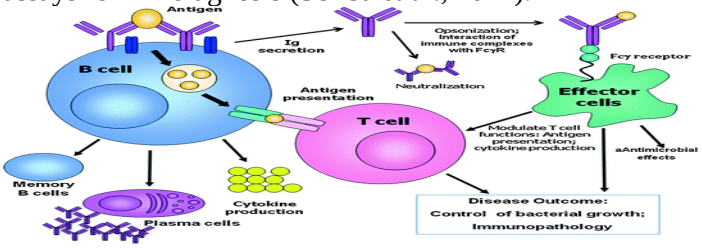

Figure 3: How do B cells modulate the immune responses to M. tuberculosis?

Production of M. tuberculosis-specific antibodies can mediate the formation of an immune complex that can modulate the functions of effector cells such as dendritic cells and macrophages. It remains to be demonstrated whether specific neutralizing antibodies exist. B cells can serve as antigen-presenting cells to influence T cell activation, polarization, and effector functions and the establishment of T cell memory. B cells can also modulate the functions of granulomatous immune cells. In concert, these antibody-dependent and independent functions of B cells play an important role in determining disease outcome in terms of the elimination of control of bacteria, as well as the development of immunopathology that could damage tissues and promote dissemination (L. kozakiewicz *et al*., 2013).

3.2. Antibody Quality

The primary purpose of antibody measurement has been the diagnosis of TB disease, and most studies focus on the number of antibodies detected and not antibody quality. Antibody avidity is variable in TB patients (Maes RF, 1991), and shortly following TB treatment, there is an increase in antibody quantity and a decrease in avidity, suggesting exhaustion of the B cell response (Aris-Bouda LM *et al*., 2003). A decrease in avidity of antibody specific for the live cell surface of mycobacteria in TB patients, suggesting conversion of antibodies to low avidity IgG or B cell exhaustion (Perley *et al*., 2014). Antibody avidity was also higher in those previously immunized with BCG, which raises the possibility of using vaccination to improve antibody avidity as a potential mechanism for protection against TB (Scriba *et al*., 2017).

3.3. Variation in Human Antibody Responses against Mycobacterium Tuberculosis

It has long been known that natural infection induces the formation of antibodies against MTB (Jacobs et al., 2016). Studies demonstrated that 90% of TB patients have raised titers of serum immunoglobulin against mycobacterial antigens at the time of clinical presentation (Lyashchenko et al., 1998). The correlation between antibody responses and active TB disease led to an investigation of antibodies as diagnostic markers rather than a therapeutic strategy, but these efforts were discouraged by the WHO in 2012, due to suboptimal sensitivity and specificity in studies (WHO, 2021).

3.4. Isotypes and Subclasses of Antibodies to Mycobacterium Tuberculosis Infection

Within the broadest of strokes, antibody titers increment as Mycobacterium tuberculosis burden increments, apparently due to expanded antigen accessibility (De- Araujo et al.,

2018). More particularly, a few but not all think about appearing that dynamic aspiratory TB inspires Mycobacterium tuberculosis particular IgG isotype reaction with the rise of both Mycobacterium tuberculosis -particular and add up to IgG1 and IgG3 subclasses in serum (De-Araujo et al., 2018).

In vitro, IgG1 mediates TNF-α discharge from human monocytes but does not increment the anti-inflammatory cytokine IL 10 (Hussain et al., 2001). Reliable with these affiliations, complement C1q levels are higher in dynamic TB compared to inactive TB, and complement cascade particles are up-regulated 18 months sometime recently movement from Mycobacterium tuberculosis infection to TB disease (Lubbers et al., 2018). In addition, a few monoclonal Mycobacterium tuberculosis IgG1 can upgrade bacterial replication in vitro, illustrating the potential to worsen illness (Zimmermann et al., 2016).

Notably, the defensive impact shows up to be revoked with the enzymatic evacuation of glycan buildups (Olivares et al., 2013). Hence, Mycobacterium tuberculosis receptive IgG with intact glycosylation in complex polyclonal reactions may take an interest in controlling bacterial burden (Milla et al., 2019). Beyond IgG, IgA has been a center of interest due to the significance of this isotype in mucosal immunity inside the aspiratory compartment, the most courses of TB infection, acquisition, and ensuing transmission (Milla et al., 2019). Monoclonal IgA was able to repress Mycobacterium tuberculosis development, whereas IgG antibodies to the same targets advanced disease (Zimmermann et al., 2016). Intriguingly, this isotype-mediated control of MTB appears to be modulated via FcαR/FcγR independent mechanisms (Milla et al., 2019).

3.5. Antibodies as Potential Biomarkers for Protective Immunity against Mtb

Individuals with persistent negative TSTs, despite years of exposure to ATB patients, had elevated anti-Mtb IgG levels, and their serum was able to block proliferation of peripheral blood mononuclear cells in response to protein purified derivatives (PPD) (171). In concordance, highly exposed, but TST-negative, individuals displayed high anti-PPD Abs titers, which inhibited autologous T-cell proliferation after PPD stimulation (172). Abs specific for CFP-10 and ESAT-6 in Quantiferon TB Gold (QFT) supernatants independently separated LTBI from ATB (173). More recently, Lu et al. reported that highly exposed, but TST- and IFN-γ release assay (IGRA)-negative, individuals harbored Mtb-specific IgM and IgG, while diminished CD4-mediated IFN-γ responses directed toward Mtb early secreted Ag of 6 kDa (ESAT-6), 10 kDa culture filtrate protein (CFP-10), Ag85A and Ag85B were found (163). Taken together, these studies implicate that humoral immunity is detectable infrequently exposed individuals with persistently negative skin testing or QFN evaluation, which represent read-outs of effector T-cell responses. In such settings, Abs may be considered biomarkers of protective immunity.

4. Antibody-mediated protection

4.1. Humoral Immunodeficiency and Risk of Tuberculosis

HIV is known to cause immune dysfunction, rendering HIV/TB-co-infected individuals more susceptible to progression to ATB (Esmail *et al*., 2018; Gupta *et al*., 2015). Specifically, progressive untreated HIV infection is associated with a loss of total (Esmail *et al*., 2018) and M. tuberculosis-specific CD4 T cells (Yao *et al*., 2014). Given the critical role of CD4 T cells in the control of TB in mice (Lin, 2012), depletion of T cells is likely to contribute to the development of ATB in HIV-infected individuals.

Genetic susceptibility to mycobacterial disease is well described and is typically seen in the loss of functionality in the IL-12, STAT1, and IFN-γ pathways (Cottle, 2011). IFN-γR1 deficiency resulting from homozygous or compound heterozygous null mutations in *IFN-γR1* causes severe, often fatal infection (Newport *et al*., 1996; Jouanguy *et al*., 1997; Altare *et al*., 1998). A homozygous null mutation in *IFN-γR2* also results in severe atypical mycobacterial infection (Dorman and Holland, 1998). In both deficiencies, granulomas fail to form in tissues. Both the binding (IFN-γR1) and signaling (IFN-γR2) chains of the IFN-γ receptor are essential for IFN-γ mediated signaling and control of mycobacterial infection. In partial IFN-γR1 deficiency, the IFN-γR1 is expressed on monocytes but has reduced ligand affinity (Jouanguy *et al*., 1997). In contrast, to complete IFN-γR1 deficiency, this reduced IFN-γ signaling is sufficient for the organization of granulomas, and the clinical course is milder.

4.2. Antibodies in Prevention of Infection with Mycobacterium Tuberculosis

Antibodies that have been obtained from persons with latent tuberculosis and those with active tuberculosis have functional differences in vitro. Antibodies from peripheral-blood cells of persons with the latent disease and active disease have the efficacy of inhibiting Mycobacterium tuberculosis infection in macrophages and epithelial cells (Lu *et al*., 2016 and Zimmermann *et al*., 2016). IgG from persons with the latent disease was more effective at inhibiting mycobacterial growth in macrophages than IgG from persons with active disease (Lu *et al*., 2016). IgA isotypes inhibited infection of an epithelial cell line and the IgG isotypes promoted infection (Zimmermann *et al*., 2016).

4.3. Monoclonal Antibody Studies during Mycobacterium Tuberculosis Infection in Mice

The defensive impact of monoclonal antibodies focuses on three well-known MTB antigens: heparin-binding hemagglutinin (HBHA), alpha-crystallin, and arabinomannan (AM), the sugar component of the glycolipid lipoarabinomannan (LAM) (Clemens, H, and Carolyn, G. King, 2021). Monoclonal antibodies decreased bacterial burden, improved control of microbes, or diminished lung pathology (Balu *et al*., 2021). HBHA is a surface-exposed protein that interacts with proteoglycans and can facilitate MTB entry into epithelial cells *in vitro* (Locht *et al*., 2006).

During infection, HBHA was shown to be required for extrapulmonary dissemination, as mucosal administration of MTB lacking HBHA expression impaired its ability to spread to other organs, such as the spleen (Pethe *et al*., 2001). Similar to HBHA, LAM is found within the bacterial cell envelope and constitutes a major component of the cell wall (Clemens, H, and Carolyn, G. K, 2021). Alpha-crystallin (too called 16-kDa antigen or HspX) may be a cytosolic protein that has moreover been recognized within the cell envelope of MTB (Hermann *et al*., 2021). Accordingly, alpha-crystallin is essential for bacterial survival during periods of disease latency when MTB also undergoes metabolic adaptation to survive under conditions of oxygen deprivation, nutrient depletion, and low pH (O'Toole *et al*., 2018).

4.4. Potential Mechanisms of Antibody-Mediated Immunity in Tuberculosis

Despite being a facultative intracellular pathogen, MTB is potentially susceptible to various mechanisms of antibody-mediated immunity. Opsonization through FcγR was shown to promote phagolysosomal fusion (Armstrong and Hart, 1975) and to increase macrophage Ca2+ signaling and intracellular killing (Malik *et al*., 2000). IgG bound to BCG increased the release of oxygen in the phagosomes of alveolar macrophages, suggesting the enhancement of antimycobacterial macrophage activity by antibody (Suga *et al*., 1996). Immune complexes that stimulate

FcεRII CD23 receptors trigger has been associated with antimycobacterial activity (Mossalayi *et al*., 2009).

Furthermore, the existence of potentially synergistic functions between humoral and cell-mediated immunity against TB is suggested by the observation that anti-mycobacterial antibodies in BCG-vaccinated persons enhance both innate and cell-mediated immune responses against mycobacteria (de Vallière *et al*., 2005) and that sera from TB contacts with high but not low IgG titers against tuberculin can block proliferation of PBMC cultures with tuberculin (Encinales *et al*., 2010). Moreover, a robust T cell response against mycobacteria is enhanced by specific antibody responses that can augment Th1 activation via FcR by facilitating rapid uptake, processing, and presentation of antigens (Igietseme *et al*., 2004).

The antibody can also contribute to the host defense against MTB by promoting the clearance of immunomodulatory antigens such as LAM (Glatman-Freedman *et al*., 2000). Finally, antibodies that mimic the action of fungal killer toxins are bactericidal to M.tb (Conti *et al*., 1998). Although such antibodies are unlikely to be present in MTB infection, the fact that mycobacteria can be killed directly by certain antibodies provides a precedent for such a mechanism of antibody-mediated protection.

In addition to these direct mechanisms, antibodies can influence the outcome of mycobacterial infection through their ability to modulate inflammation. Some antibodies, such as IgM, can demonstrate pro-inflammatory properties through their ability to activate complement (Ciurana *et al*., 2004), while other antibodies, such as IgG, can demonstrate pro- or anti-inflammatory properties depending on the antigen and FcR receptor engaged (Ballow, 2011; Lux *et al*., 2010).

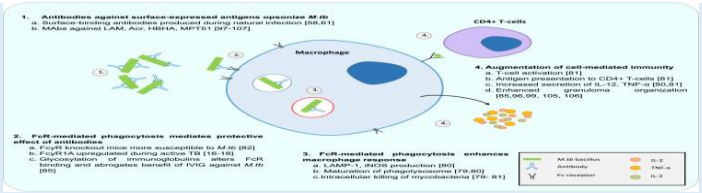

Figure 4: Antibodies modulate MTB-macrophage interaction via FcR mediated phagocytosis.

Antibodies are now also understood to augment CMI and reduce the survival of intracellular pathogens via effector functions of the Fcγ receptor (FcR) (Tameris *et al*., 2013).

4.6. Mucosal Protection against Tuberculosis

It is well known that the mucosa is the largest immune organ in the body, and it is generally believed that almost all infectious diseases are initiated at the mucosal surface (Ye *et al*., 2011). The respiratory tract is the natural route for Mtb infection, where Mtb infects the individual mainly through the mucosal tissue of the respiratory tract after inhalation of mycobacteria containing droplets from the external environment. Normally, the pathogen (Mtb) infection could be eliminated by the host's immune system, but it is desirable to induce immunity before the infection through vaccination in most cases. To effectively prevent Mtb infection, the approach of mucosal immunization has recently received increasing attention in the field of tuberculosis vaccination owing to its potency in inducing mucosa-associated protection from mucosal infectious diseases (Ogra *et al*., 2001). Several lines of evidence have suggested that mucosal immunity can provide unique advantages for protection against mycobacterial infection, by which the immune cells, such as macrophages, dendritic cells, and leukocytes recognize the pathogen-associated molecular patterns (PAMPs), and sequentially activate the anti-mycobacterial immune responses including the activation of specific T-cell and antibody synthesis (Mogensen, 2009).

Mice missing the polymeric Ig receptor which transports IgA into the respiratory mucosa are more helpless to MTB infection than wild-type mice (Tjarnlund *et al*., 2006). In a novel try, polyclonal human secretory IgA (hsIgA) was decontaminated from colostrum given by healthy women and appeared to contain IgA able to tie entirety BCG and MTB lysate (Alvarez *et al*., 2013).

Prophylactic intra-tracheal incubation or pre-incubation of MTB with this hsIgA diminished bacillary stack and moved forward granuloma arrangement within the lungs of mice challenged with live MTB (Alvarez *et al*., 2013). This appeared that antibodies able of interacting with MTB within the mucosa may be passively passed on between mother and child, which human MB particular hsIgA can alter the course of disease (Alvarez *et al*., 2013).

4.7. Antibody Function in Mycobacterium tuberculosis

With differential glycosylation, isotypes, and subclasses, antibody Fc-domain engagement of Fc receptors on immune cells helps modulate pro- and anti-inflammatory signals, the balance of which, in TB, can contribute to outcome (Hogarth, 2012). Despite lower Mycobacterium tuberculosis particularly IgG titers in inactive compared to active TB, there is a higher affinity for the activating FcγRIIIa and no difference in the activating FcγRIIa or inhibitory FcγRIIb (Lu *et al*., 2016).

Studies in mice deficient of the inhibitory FcγRIIb have greater control of MTB bacterial burden, whereas complete knock out of the Fcγ chain region, which is essential for activating FcγR signaling, resulted in more severe disease in pulmonary pathology (Maglione *et al*., 2008). Furthermore, there are higher levels of FcγRI receptor quality expression in people with active TB compared to inactive TB (Sutherland *et al*., 2014), and these levels diminish throughout therapy (Cliff *et al*., 2013). FcγRI is an activating receptor, which is upregulated by cytokines such as IFN-γ and GM-CSF and binds with high affinity to IgG1, IgG3, and IgG4 in comparison to the low-affinity FcγRIIIa or IIa (Hogarth, 2012).

As such, high FcγRI levels in active TB may either be a marker of or contribute to the inflammation. At a cellular level, immune cells expressing Fc receptors have been implicated in both the enhancement of bacterial uptake, as well as the control of bacterial fate, in the context of antibodies (Milla *et al*., 2019). In studies with human cells and Mycobacterium tuberculosis, macrophages, NK cells, and alveolar epithelial cells have been illustrated to both possibly repress additionally upgrade bacterial development within the setting of antibodies (Milla *et al*., 2019).

Be that as it may, upon the expansion of filtered polyclonal IgG after Mycobacterium tuberculosis disease, the intracellular bacterial burden is diminished within the setting of antibodies from inactive compared to active TB people (Lu *et al*., 2016). Particularly, the classical antibody-inspired effector capacities of NK cell actuation and consequent generation of granulysin to interceded ADCC have been watched (Lu *et al*., 2016; Roy *et al*., 2018).

Additionally, phagolysosomal fusion, inflammasome activation, and IL-1β production could be elicited more with polyclonal IgG purified from individuals with latent compared to active TB (Lu *et al*., 2016). Typically steady with monoclonal antibodies upgrading BCG lysosomal colocalization (Joller *et al*., 2010). Pre-hatching with human serum containing mycobacterial particular IgG and IgM encourage upgrades to complement authoritative to mycobacteria (Carrol *et al*., 2009).

4.8. The Antibody Reaction after Immunization

Mucosal or intravenous BCG inoculation in macaques was too as of late appeared to actuate close sterilizing resistance to MTB infection challenge, connecting with an increment in MTB-specific IgG, IgA, and IgM antibodies within the blood and bronchoalveolar lavage liquid (BAL) liquid (Dijkman *et al*., 2021).

IgG and IgM antibodies separated from the BAL of BCG immunization macaques have in this way been appeared to opsonize MTB and upgrade bacterial take-up by macrophages *in vitro* (Dijkman *et al*., 2021). Notably, MTBVAC—a live weakened MTB inferred immunization that evokes more vigorous and fast versatile resistant reactions compared with BCG (Dijkman *et al*., 2021).

Interestingly, oral administration of BCG led to increased anti-LAM IgA titers in tears, underscoring its capacity to induce mucosal antibody responses (Brown *et al*., 2003). Another ponder on intradermal BCG inoculation of members detailed increased AM-specific IgG reactions within the serum, which correlated with opsonization and killing of BCG by human macrophages (Chen *et al*., 2016).

Here, elevated Ag85A-specific IgG within the serum is related to diminished hazard of illness after BCG inoculation (Fletcher *et al*, 2016). At long last, and comparative to MTB disease, BCG immunization was appeared to initiate high avidity IgG antibodies to bulk surface antigens, like tuberculosis glycolipid (Nabeshima *et al*., 2015).

4.9. Antigens Targeted by Humoral Immunity during Tuberculosis Infection

Nevertheless, the foremost regularly recognized antigens for serological think about incorporating alpha-crystallin, HBHA, AM/LAM, antigen 85 (Ag85), PstS1, LpqH, MPT32, and malate synthase G (Steingart *et al*., 2009). Most of these antigens are recognized within the cell envelope and are at the slightest somewhat included in bacterial interaction with macrophages. Most of these antigens are at the slightest incompletely found within the

cell envelope of MTB, highlighting the significance of this layer in creating antibody reactions amid disease (Clemens Hermann and Carolyn G. King, 2021).

The Ag85 complex, consisting of the subunits Ag85A, Ag85B, and Ag85C, is a secreted protein that also exhibits cell wall glycosyltransferase activity and is required for the biosynthesis of cord factor, a virulent glycolipid that drives granuloma formation (Belisle *et al*., 1997). Ag85 has a high affinity for fibronectin and facilitates the attachment of MTB to murine alveolar macrophages. PstS1 is a surface-exposed lipoprotein involved in the uptake of inorganic phosphate, an essential but often limiting nutrient in the microenvironment. Like Ag85, PstS1 can also act as an adhesin for binding to human and mouse macrophages (Esparza *et al*., 2015).

LpqH, another cell surface-exposed antigen, is a glycoprotein that acts as a TLR2 agonist, inducing up-regulation of MHC II and cytokine secretion by macrophages (Greenway *et al*., 2005; Nossa *et al*., 2001). The antigen MPT32 is secreted by MTB early on during disease progression but has also been detected in the cell envelope fraction of MTB. MPT32 functions as an adhesin and is suggested to be involved in the invasion of epithelial cells (Abeba *et al*., 2007). Lastly, malate synthase G is a cytosolic protein that functions in glycolate metabolism and elicits strong antibody responses during active TB (Laal *et al*., 1997).

Most of these antigens are at least partly located in the cell envelope of MTB, highlighting the importance of this layer in generating antibody responses during infection. In general, antibodies that bind to cell-surface exposed antigens can lead to opsonization, thereby impacting bacterial uptake and intracellular trafficking by phagocytic cells (Clemens Hermann and Carolyn G. King, 2021).

4.10. Attempts to Connect Antibody Specificity and Tuberculosis Illness

MTB disease is clinically tested by two tests: the tuberculin skin test (TST) and the interferon-γ (IFN-γ) release assay (IGRA). The TST involves an injection of PPD into the skin, which results in a delayed-type hypersensitivity reaction in individuals with previous MTB exposure or infection. IGRA measures IFN-γ production by MTB-specific T cells following *ex vivo* stimulation with MTB peptides, ESAT6, and CFP10 (Clemens Hermann and Carolyn G. King, 2021).

Individuals who stay TST and IGRA despite high presentation to individuals with clinically analyzed MTB have been named ‘resisters’ or ‘long-term controllers’ (Simmons *et al*., 2018). Antibodies from the serum of resisters were responsive to PPD, Ag85, ESAT6/CFP10, alpha-crystallin, GroES, and LAM (Clemens Hermann and Carolyn G. King, 2021). Although the specificities of antibodies isolated from resisters and individuals with latent TB infection were largely overlapping, bulk PPD-specific antibody responses in resisters were qualitatively distinct from individuals with latent TB, with higher avidity IgG and higher titers of antibodies capable of eliciting IFN-γ secretion of NK cells (Lu *et al*., 2019).

Although glycosylation of the Fc antibody domain regulates IgG structure and effector function, the link between glycosylation and function reflects changes in antibody specificity. Increased galactosylation that correlates with reduced antibody efficacy during active TB could represent the expansion of nonspecific plasma cells, which poorly target MTB (Clemens Hermann and Carolyn G. King, 2021).

MTB-specific plasma blasts appeared a high recurrence of IgA+ B cells proposing their mucosal root. Importantly, IgA antibodies were able to prevent epithelial cell infection in vitro while IgG antibodies with identical specificity either promoted infection or had no effect (Clemens Hermann and Carolyn G. King, 2021). In MTB infection, the high plenitude of IgG and IgA plasma cells within the lung is connected with a high bacterial load (Gideon *et al*., 2020). IgG antibodies focusing on AM in latently infected patients were found to upgrade take-up of MTB and intracellular killing by human macrophages *in vitro*. This impact was subordinate to anti-AM-specific antibodies since consumption of AM particular antibodies repealed the impact (Chen *et al*., 2020).

5.Potential future directions for antibody research in tuberculosis

Future applications of antibody formulations for the control of TB may include several possibilities including treatment, prevention, and diagnosis.

5.1. Treatment

Antibody-based therapy could potentially be useful in several scenarios. They could be used to shorten the standard treatment period of patients with uncomplicated TB when coupled with standard chemotherapy. However, they would be particularly important in the treatment of patients infected with Multi-drug Resistant (MDR) and Extensively Drug-Resistant (XDR) strains, in combination with the standard treatment (Armando *et al*., 2017).

Monoclonal antibodies against the surface of Methicillin-resistant Staphylococcus Aureus (MRSA) have very recently been used to deliver antibiotics directly to host cells, where MRSA appears to establish intracellular reservoirs to evade host immunity (Lehar et al., 2015). Utilizing comparable novel antibody-antibiotic conjugate innovation, Mabs seem possibly to be adjusted to provide drugs straightforwardly to TB-infected have cells (Ashley *et al*., 2016).5.2. Prophylactic use

Prophylactic use of antibodies could be applied in recent contacts of TB patients, with special attention to risk groups (Norazmi *et al*., 2005). In this regard, successful prophylactic use of antibodies in exposed individuals has been shown in the case of several other pathogens such as varicella, tetanus, Respiratory Syncytial Virus (RSV), rabies, and Hepatitis B (Casadevall *et al*., 2004).

5.3. Vaccines

The induction of specific protective antibody responses by vaccination, either alone or as an addition to the stimulation of cell-mediated immunity could be a novel strategy for the development of the new generation of prophylactic and therapeutic vaccines against TB.

The prevailing past dogma that discounted the role of antibodies in host protection against TB has resulted in a limited study of B cell immunodominant epitopes as targets for protective immunity (DeGroot et al., 2005).

5.3.1. Polysaccharide conjugate vaccines

Polysaccharide conjugate vaccines are considered to elicit specific protective antibody responses against a variety of pathogens (Pollard *et al*., 2009). However, the polysaccharide conjugate vaccine against Salmonella typhi (Thiem *et al*., 2011) demonstrates the feasibility of this kind of vaccine for the prevention of infectious diseases caused by intracellular pathogens. In the case of M. tuberculosis, several authors reported the use of polysaccharide conjugated vaccine candidates (Glatman Freedman *et al*., 2004). Arabinomannan protein conjugate immunization initiated both antibody and T-cell reactions. Counteraction of LAM-induced T-cell suppression and inhibition of macrophage function by an antibody is another potential mechanism (Hamasur *et al*, 2003).

All these vaccine candidates induced the production of specific IgG (Schwebach *et al*., 2002) and some of them conferred variable levels of protection (Hamasur *et al*., 2003) which validate this strategy as one of the potential avenues for the development of a new generation of vaccines against tuberculosis.

5.3.2. Identifying other B-cell immunodominant epitopes

With the development of bioinformatics tools for bacterial genome analysis, it has been possible to predict in silico microbial regions that trigger immune responses relevant for protection and vaccine development. A candidate experimental vaccine based on proteoliposomes from M. smegmatis is currently in development (Rodriguez *et al*., 2011). In one study, a bibliographic search was used to identify highly expressed proteins inactive, latent, and reactivation phases of TB (LeThuy *et al*., 2010). The subcellular localization of the selected proteins was defined according to the report on the identification and localization of 1044 M. tuberculosis proteins using two-dimensional, capillary high-performance liquid chromatography coupled with mass spectrometry (2DLC/MS) method (Mawuenyega *et al*., 2005) and using prediction algorithms of a new generation of vaccines against tuberculosis.

In addition to cellular immune effectors recognizing antigens from M. tuberculosis, cross-reactive humoral immune responses of several IgG subclasses corresponding with a combined Th1 and Th2 pattern against antigenic components of M. tuberculosis were elicited. These findings were in concordance with the in silico predictions (LeThuy *et al*., 2010). It is interesting to note that differences in the pattern of humoral recognition of lipidic components were dependent on the characteristics of the adjuvant used, which could have relevance for the development of vaccines that includes lipidic components (Rodriguez *et al*., 2011).

Bioinformatics tools for the prediction of T and B epitopes were also employed for the design of multi-epitopic constructions, which were used to obtain recombinant BCG strains. Based on this prediction, B cell epitopes from ESAT-6, CFP-10, Ag87B, and MTP40 proteins were selected and combined with T cell epitopes of the 87B protein and fused to Mtb8.4 protein (Acosta *et al*., 2010).Next-generation sequencing has moreover contributed to the illustration of the Antibodies collection in reaction to infection and immunization (Georgiou *et al*., 2014). This progress may permit mapping of how the antibody reaction creates amid active TB infection, and how it is subverted by MTB to avoid the arrangement of any defensive antibodies as proposed by the antigenic variety in B-cell epitopes and the need for surface-binding antibodies (Ashley *et al*., 2016). The thinks about clinical populaces who show up to be safe to securing inactive disease with MTB are too of extraordinary intrigued in arrange to get it resistance against TB (Fletcher *et al*., 2016).

5.3.3. Diagnosis

Although no serological assays are currently recommended for the diagnosis of TB (Morris, 2011), largely due to the possibility of false results and thus incorrect treatments, for many other pathogens, serological diagnostic tests have been of great value, particularly in poor countries. In some cases, antibody responses can constitute useful correlates of protection (Edwards, 2001). In the specific case of TB, several studies of the antibody response have been reported (Velayudhan and Gennaro, 2010).

There is a substantial amount of variability in antibody response to TB (Navon *et al*., 2003). This variability has been attributed to several factors. Some of these factors are associated with the pathogen (strain variation, microenvironment, and growth state of bacteria) and others are related to the host, primarily previous exposure to related antigens and host genetics [99]. However, it is important to consider that only a small fraction of the genomic regions of M. tuberculosis encoding proteins have

been explored. Currently, novel immunoassay platforms are being used to dissect the entire proteome of M. tuberculosis, including reacting protein microarrays with sera from TB patients and controls [101,102]. These studies could lead to the discovery of new antigens that may constitute suitable diagnostic markers and tools for the identification of protection correlates.

6. Conclusion and recommendations:

Infection and illness caused by MTB emphatically invigorate humoral resistance in people. Even though CMI remains the overwhelming relate of security, there's proof to recommend that antibodies may contribute, at the slightest in portion, to resistance. The nearness of antibodies against particular MTB antigens such as LAM shows up to vary in patients with pneumonic and dispersed TB.

This compares to mAbs against LAM and HBHA that can diminish the bacillary stack and avoid dispersal of mycobacterial disease. Antibodies are presently broadly caught on to tweak CMI through FcR official and especially surface-binding antibodies in cases of mycobacterial contamination in test models. It is hence of intrigued that such antibodies don't appear to be invigorated amid normal disease, and the trend in protective mAbs hence distant could be a proposal that surface official with focusing on to FcR for improvement of CMI can happen in vivo.

These discoveries point to the require for assist testing of whether antibodies may bestow predominant security in immunization by improving CMI, or can avoid contamination on the off chance that shows earlier to have experience with MTB. Numerous challenges stand in this way, such as a need for information concerning the presence of useful mAbs in people and which epitopes are likely to initiate their arrangement. Be that as it may, modern innovations presently exist to conclusively address the achievability of joining objectives to target AMI within the plan of the following generation of antibody candidates.

There's a recommendation that Antibody-based therapy could potentially be useful to shorten the standard treatment period of patients with uncomplicated TB when coupled with standard chemotherapy. The study of the antibodies application in tuberculosis opens new possibilities for future development of new vaccines, diagnostics tools, and therapies against mycobacterium tuberculosis. Discoveries will likely arise from the ongoing studies in this area that will expedite the introduction of new strategies in the fight against tuberculosis.

Conflicts of Interest:

The author declare no conflicts of interest.

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